Modélisation d'adhésions cellulaires via les cadhérines

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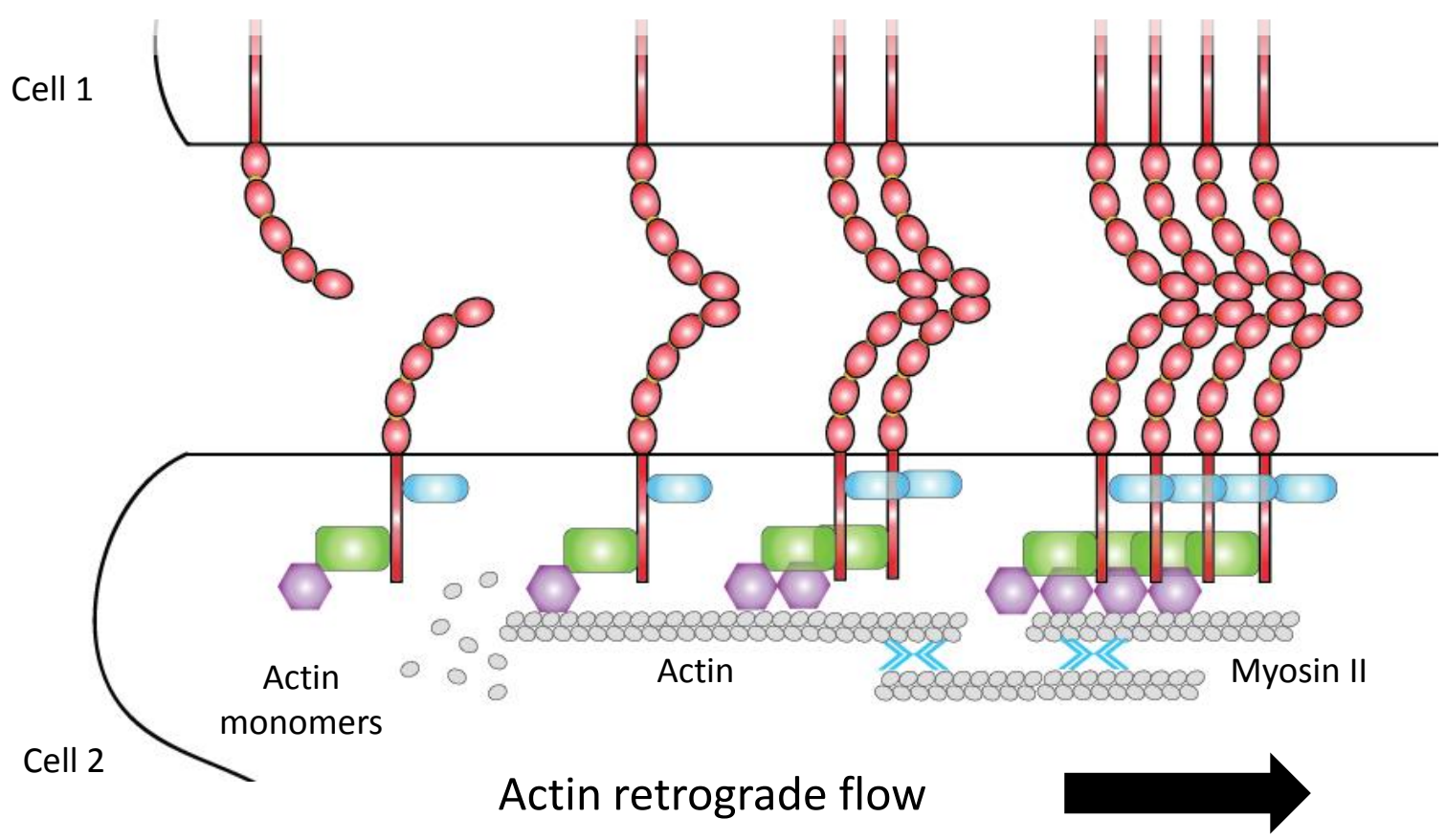
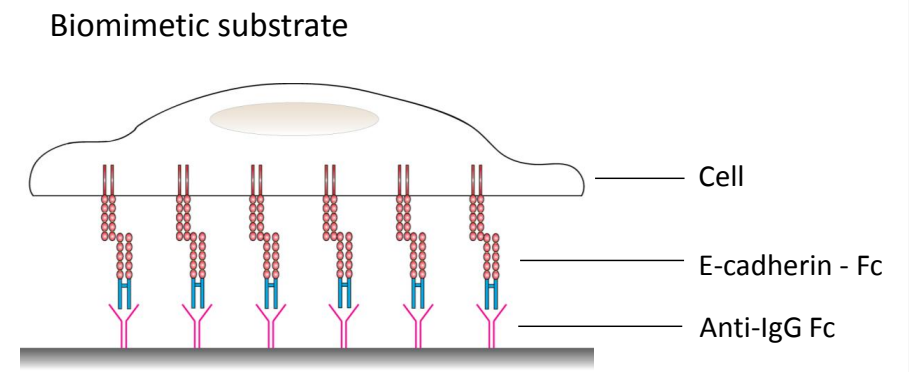
Cadherin-Cadherin adhesion and Actin



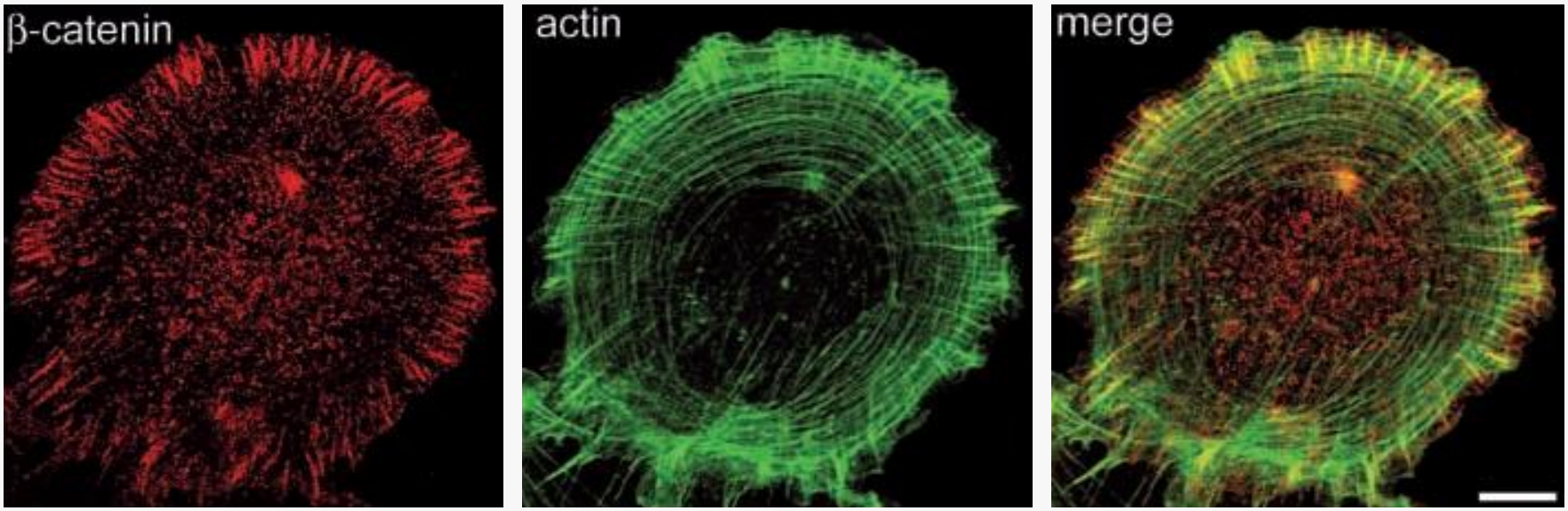
- Cadherins **diffusion**
- **Trans**- and **Cis**- contacts
- Local **aggregation** effect

- **Actin** polymerization
- **Retrograde** flow
- Cadherins **unbinding**

Experimental approach



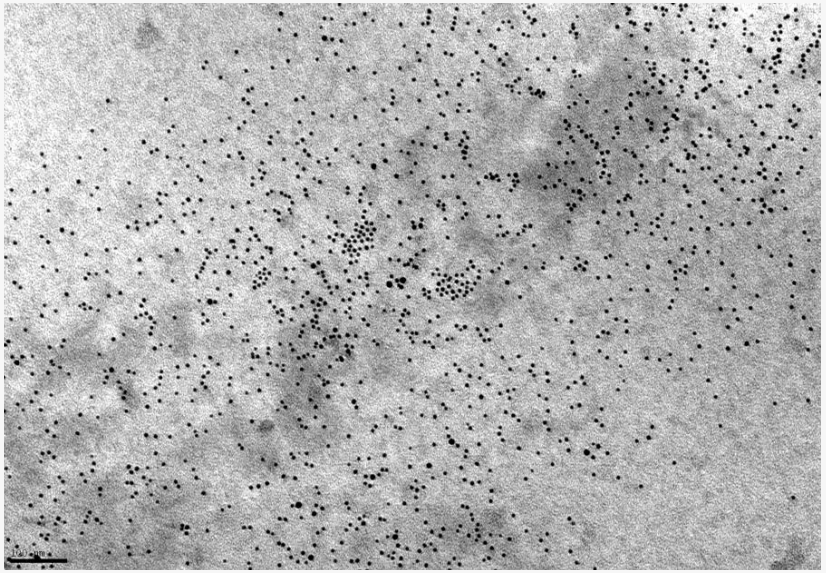
- Flat cadherins substrate
- Release of a single cell
- Spread of the cell, coating
- Fluorescence Recovery After Photobleaching (FRAP)



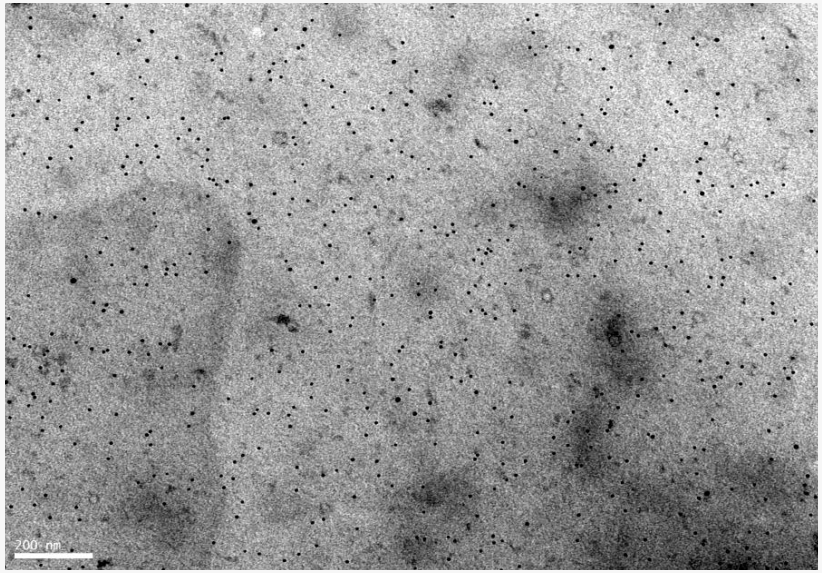
▶ Cadherins and actins has the same circular distribution

Gavard et al., **J. Cell Sci.** (2004)

Cadherin aggregate and actin



No-β-catenin inhibition



β-catenin inhibition

- With β-catenin inhibition, no polymerization, uniform distribution
- Without β-catenin inhibition, actin polymerization, radial aggregates

Cadherin diffusion and transport

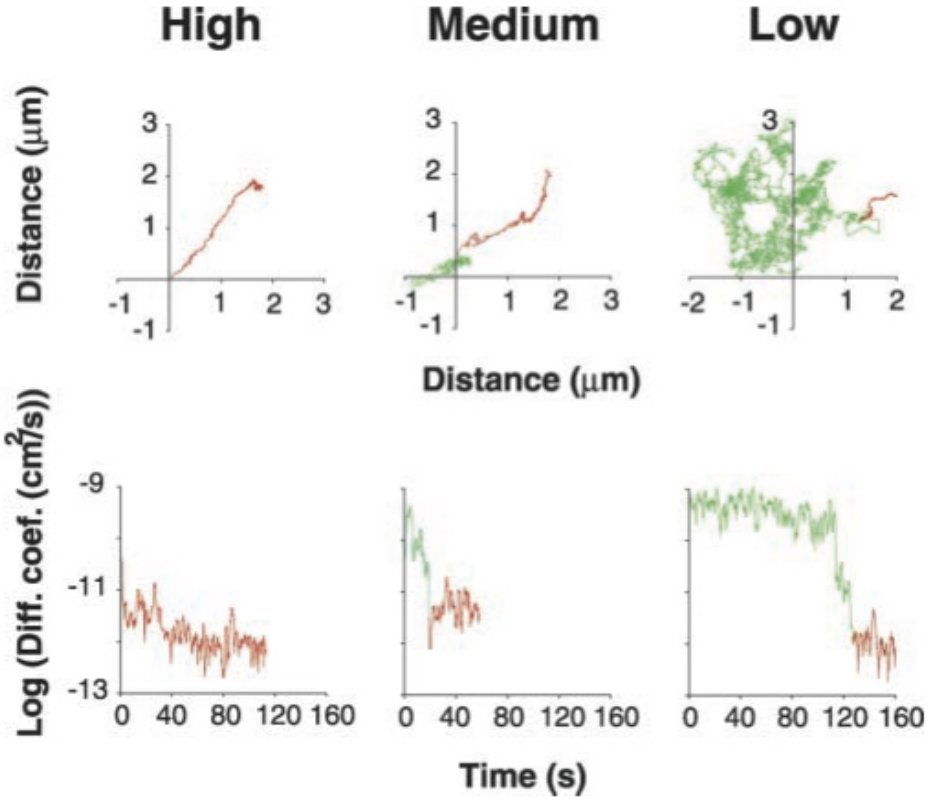


Figure 2. **Lower density Ncad-Fc beads show an initial freely diffusive phase.** Representative trajectories (X-Y plots, top) and two-dimensional diffusion coefficient versus time plots (bottom) of high, medium, and low Ncad-Fc beads. Note the biphasic behavior of the medium and low Ncad-Fc beads characterized by an initial diffusive phase (green line), followed by a sharp decrease in the diffusion coefficient and the initiation of directed movement (red line).

Lambert et al., *J. Cell. Biol.* (2002)

- Cadherins with low connection to actin filaments diffuse more than "wilde" ones.
- Green = brownian motion. Red = "transport" by actin.
- Biphasic behavior for medium and low connected cadherins.
- Diffusion coefficient for binded cadherins 2 order of magnitude smaller, almost zero.

Model #1

- Macrosc. mod. on Ω = **degenerate reaction-diffusion** syst.

$$\begin{cases} \partial_t u = \sigma \Delta u - r(u,v) \\ \partial_t v = r(u,v) \end{cases}$$

+ Homogeneous Neumann (or periodic) boundary conditions for u
+ Normalised initial data : $\int_\Omega u_0 + v_0 \; dx = 1$

- $u(t,x)$, $v(t,x)$: free and fixed cadherins densities

- Reaction term $r(u,v) \longrightarrow$ links and aggregation :

$$r(u,v) = (\rho - v) \; \Psi(v) \; u - \varepsilon \; v$$

ε unbound rate, $0 < \varepsilon \ll 1$
ρ target density (constant), $0 < \rho \leq 1 \longrightarrow 0 < v < \rho$
$\Psi(v)$ aggregation function : $\Psi(v) = a_0 + a_1 v$ with $0 < a_0, a_1 < 1$

[GGM] M. Grillot, Ph. Grillot, S. Mancini, (submitted)

Steady state of #1

- Stationary solutions (u_0, v_0) to #1 are space **homogeneous**.

$$\begin{cases} \Delta u = 0 \\ r(u,v) = 0 \end{cases} \quad \text{gives} \quad \begin{cases} u_0(x) = C \\ v_0(x) = \frac{C(a_1\rho - a_0) - \varepsilon + \sqrt{(C(a_1\rho - a_0) - \varepsilon)^2 - 4C^2\rho a_0 a_1}}{2Ca_1} \end{cases}$$

- If conservation $\int_\Omega u + v = 1$ with $|\Omega| = 1$, then

$$(u_0, v_0) = \left(\frac{\varepsilon v_0}{(\rho - v_0)(a_0 + a_1 v_0)}, v_0 \right)$$

- Linearised system:

$$\begin{cases} \lambda u + \sigma k^2 u + Au - Bv = 0 \\ \lambda v - Au + Bv = 0 \end{cases}$$

$$A = \partial_u r = \frac{\varepsilon v_0}{u_0} > 0$$

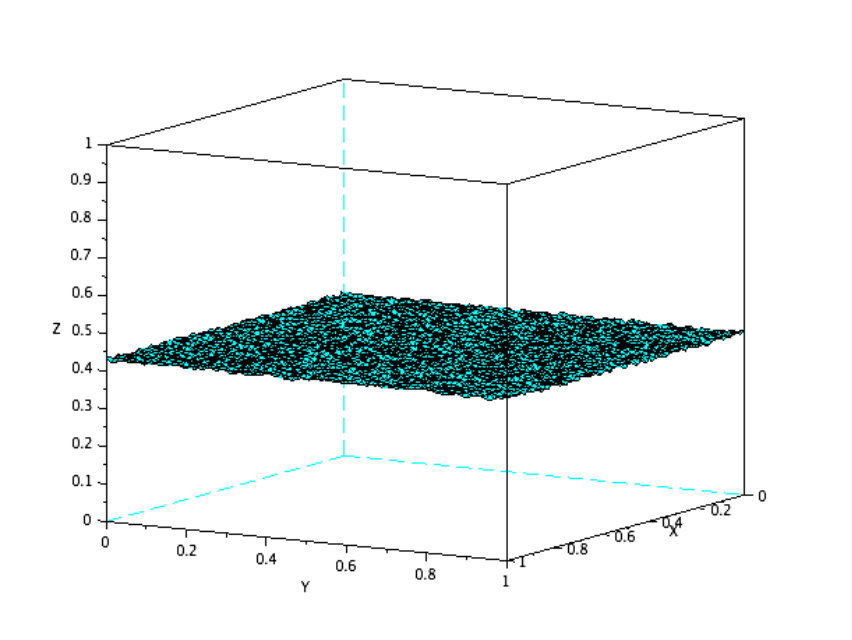
$$B = -\partial_v r = \frac{\varepsilon(a_0 + a_1 v_0^2)}{(1 - v_0)(a_0 + a_1 v_0)} > 0$$

- $\lambda_{1,2} < 0 \quad \rightarrow \quad (u_0, v_0)$ **stable** $\quad \rightarrow$ **No patterns/aggregates**

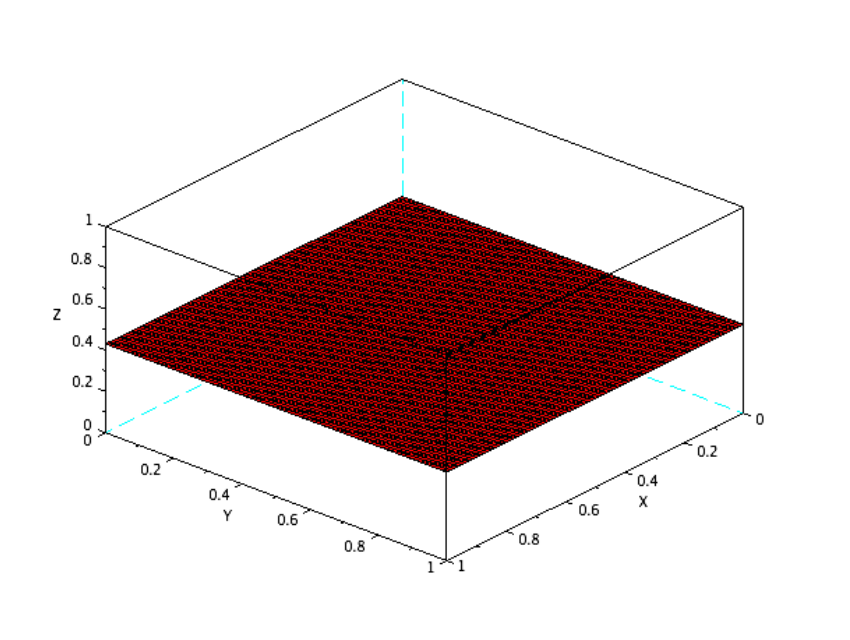
Numerical results #1

Data: $\rho = 1,\ a_0 = 0.25,\ a_1 = 0.5,\ \varepsilon = 0.35,\ \sigma = 1,\ T = 200$

$$\Rightarrow\ u_0 = 0.5691940, \quad v_0 = 0.4308060$$



perturbed initial data v_0

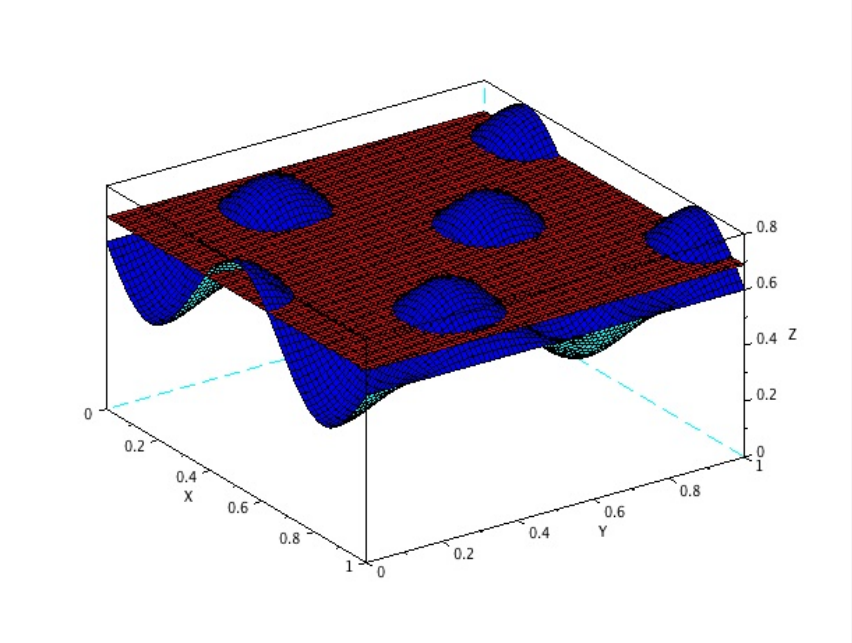


final soltion v

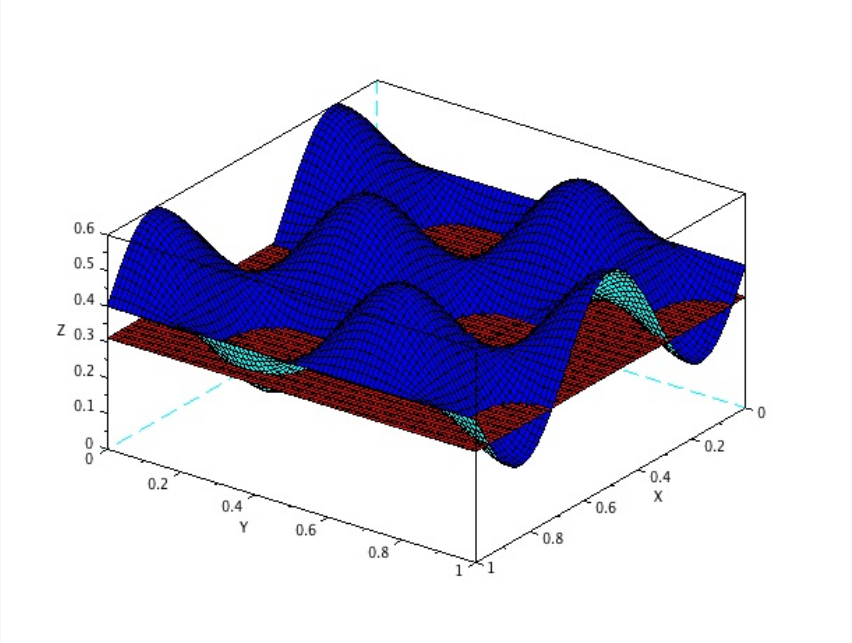
Numerical results #1

Data: $\rho = 0.7,\ a_0 = 0.25,\ a_1 = 0.5,\ \varepsilon = 0.35,\ \sigma = 1,\ T = 10$

$$\Rightarrow\ u_0 = 0.6892565, \quad v_0 = 0.3107435$$



u_0 (blue) and u (red)

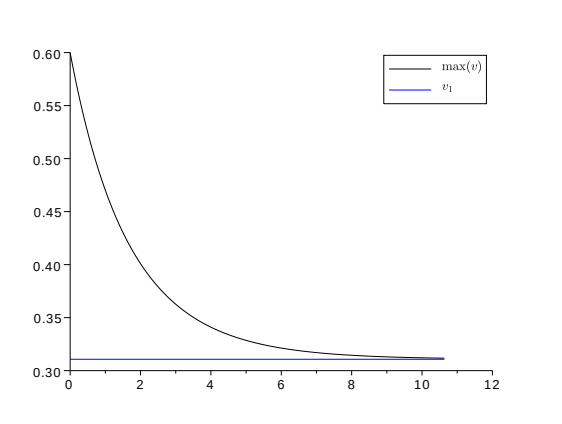


v_0 (blue) and v (red)

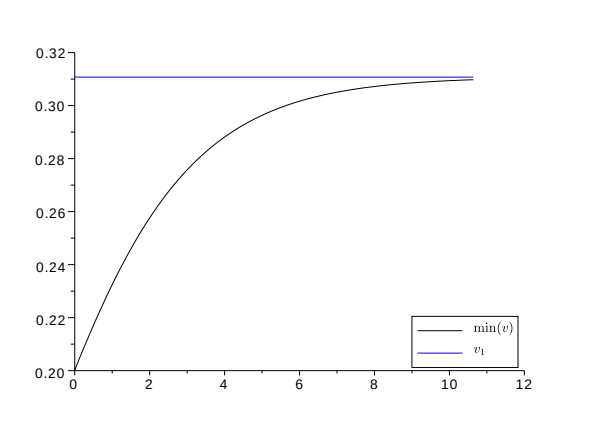
Numerical results - convergence

For the previous data, the steady state has value $\widehat{v} = 0.3107435$

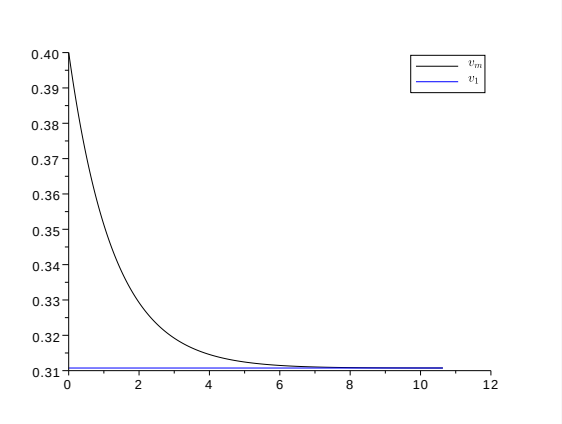
$$v_m(t) = \frac{\max v(t,\cdot) + \min v(t,\cdot)}{2}$$



v_{max}



v_{min}



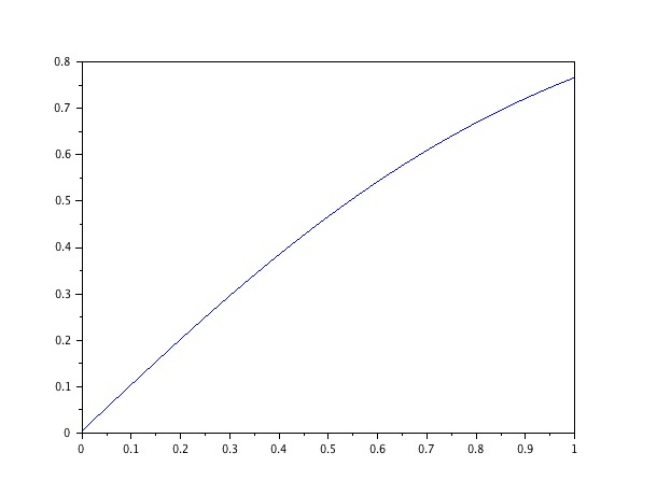
v_m

Exponential rate ?

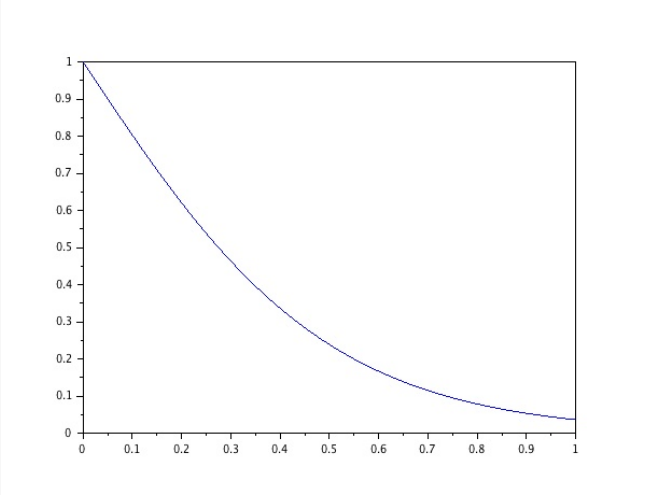
Non-linear aggregation

- if v small then small aggregation and large unbinding
- if v large then large aggregation and small unbinding

$$\Psi(v) = a + \tanh(v) \ , \qquad \varepsilon \to (1 - \tanh(bv))$$



aggregation



unbinding

The reaction term reads :

$$r(u,v) = u(\rho - v)\underbrace{(a_0 + \tanh(v))}_{F(v)} - v\underbrace{(1 - \tanh(\alpha v))}_{G(v)}$$

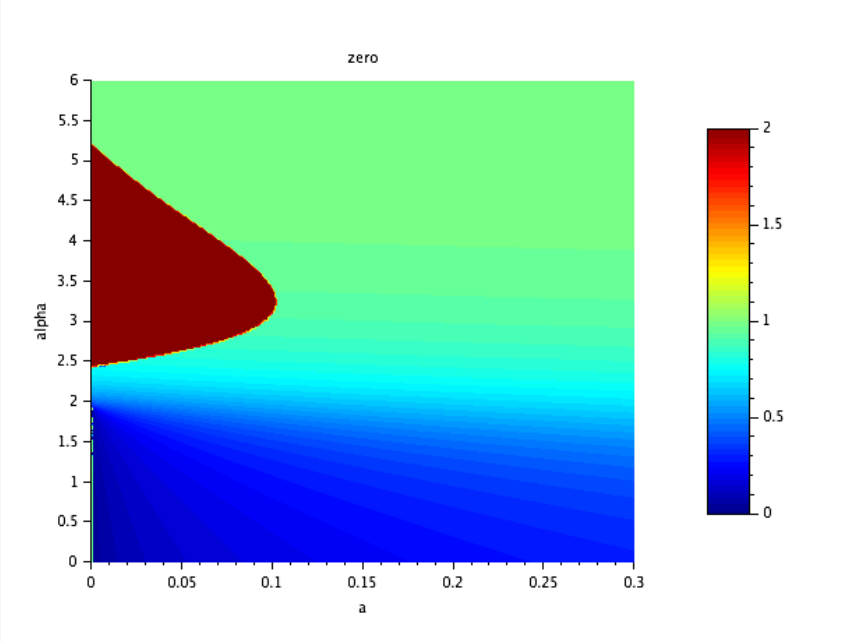
[SMMS] B. Sarels, S.Mancini, RM. Mège, PO. Strale, (in preparation)

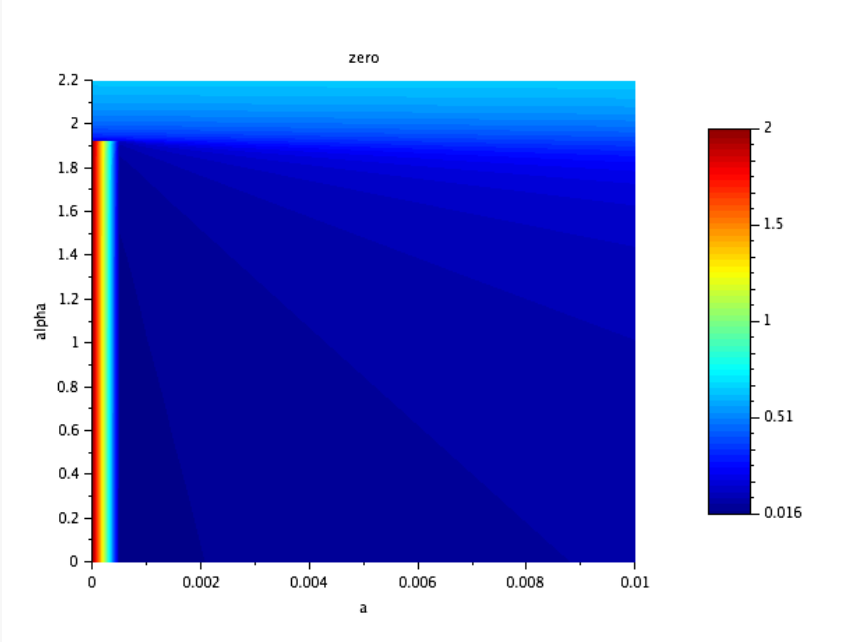
Stationary solutions

Assume $|\Omega| = 1$, $u = 1 - v$, and define

$$f(v) := (1 - v)(\rho - v)(a_0 + \tanh(v)) - v(1 - \tanh(\alpha v))$$

Since $a_0 > 0$, $f(0) = \rho a_0 > 0$, $\quad f(\rho) = -\rho(1 - \tanh(\alpha\rho)) < 0$ and $f(v)$ continuous, then $\exists\ v_0 \in [0, \rho]$ such that $f(v) = 0$.





Linearisation

- The stationary solution is **space homogeneous** :

$$\left(\frac{v_0 G_0}{(\rho - v_0)F_0}, v_0\right) \ , \quad F_0 = F(v_0) \ , \ G_0 = G(v_0)$$

- Linear system reads:

$$\begin{cases} \lambda u + \sigma k^2 u + Au + Bv = 0 \\ \lambda u - Au - Bv = 0 \end{cases}$$

with $A = (\rho - v_0)F_0 \ , \quad B = \dfrac{v_0(\rho - v_0)(F_0' G_0 - F_0 G_0') - \rho F_0 G_0}{(\rho - v_0)F_0}$

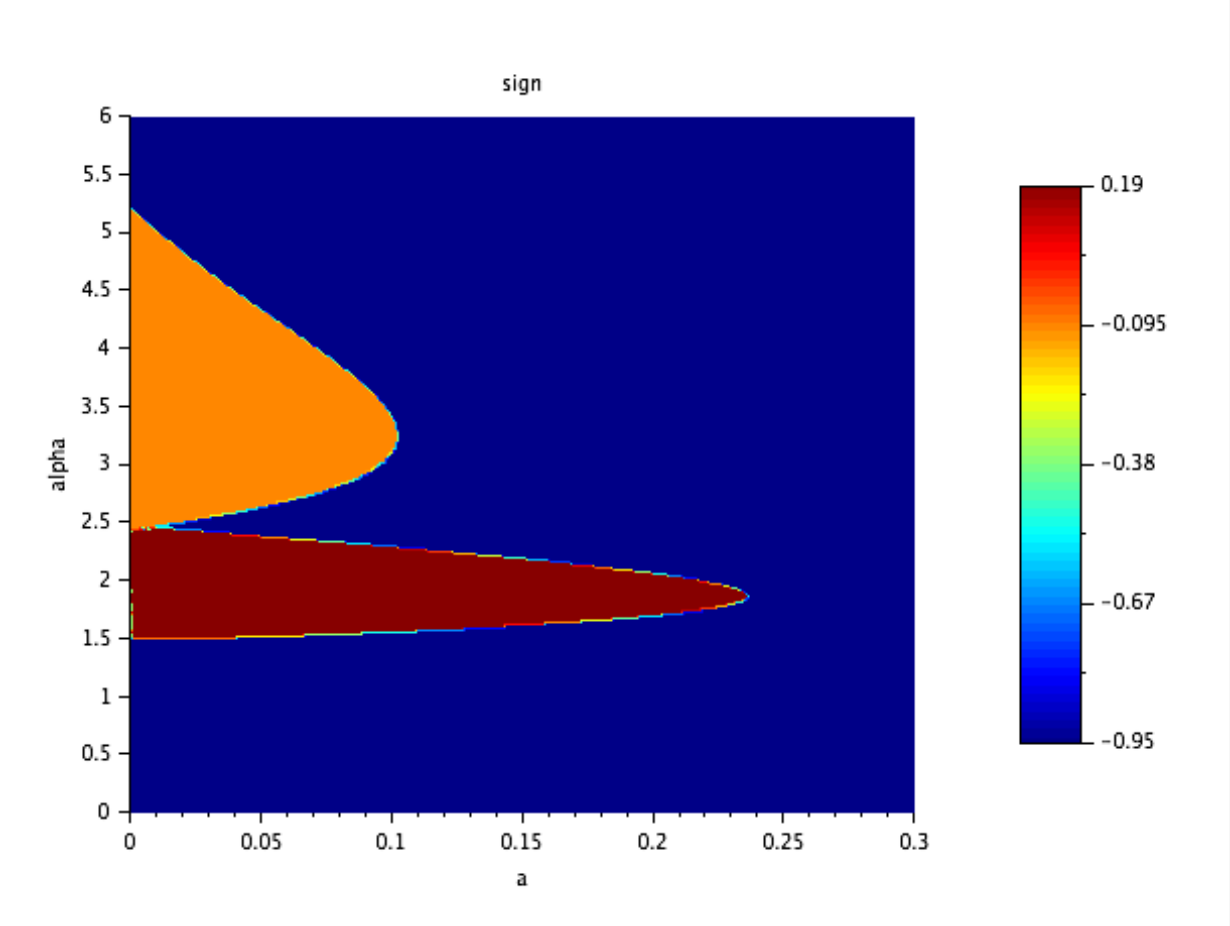
- The eigenvalues are given by:

$$\lambda = \frac{1}{2}\left(-(A + \sigma k^2 - B) \pm \sqrt{(A + \sigma k^2 - B)^2 + 4B\sigma k^2}\right)$$

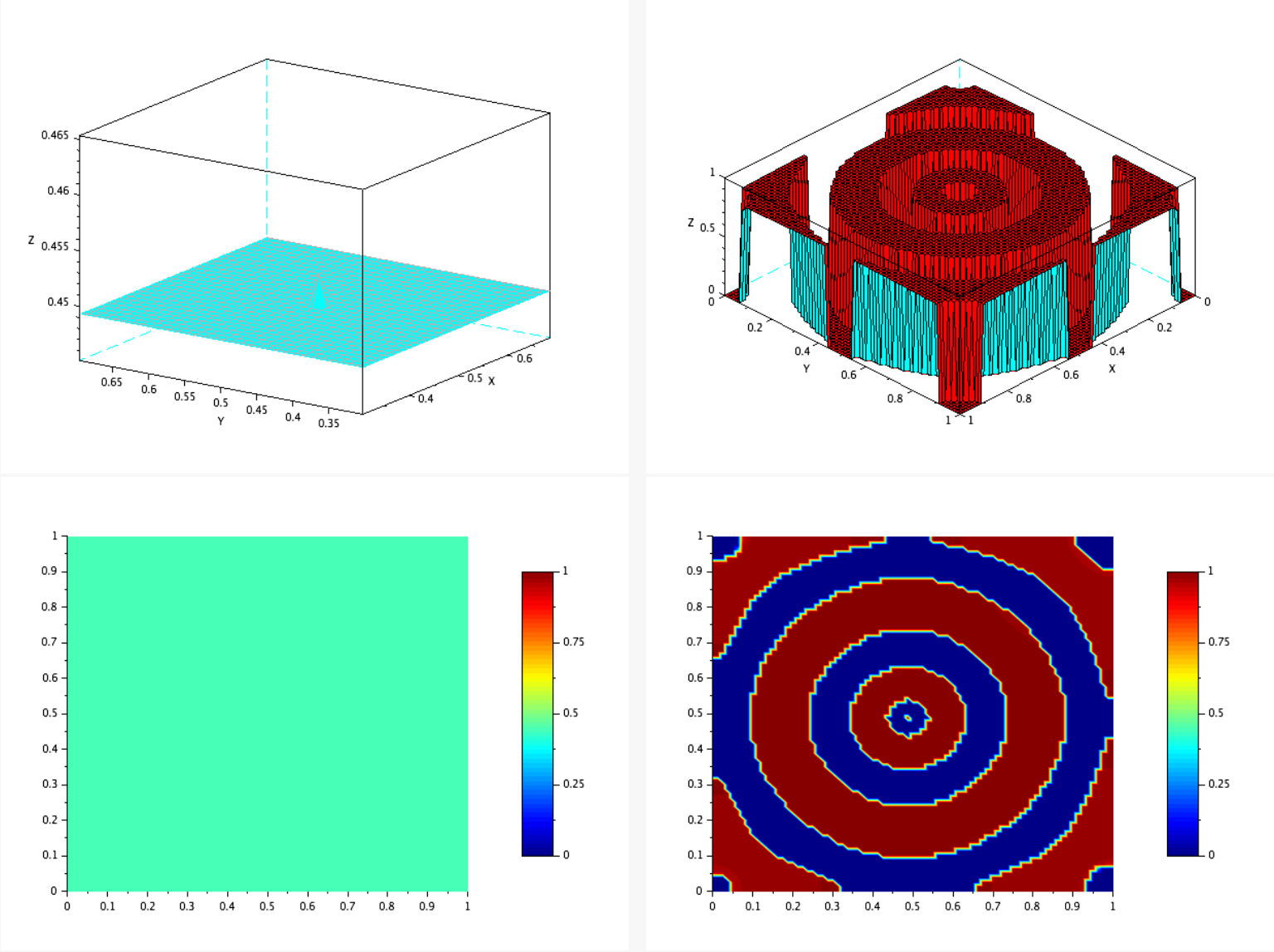
and their sign depends on the sign of B. Note $A > 0$.

Sign of B

- If $B \leq 0$, then (u_0, v_0) stable $\longrightarrow$ blue domain
- If $B > 0$, then (u_0, v_0) unstable $\longrightarrow$ red domain $\longrightarrow$ patterns formation
- If $v_0 > \rho$, then non admissible solution $\longrightarrow$ orange domain

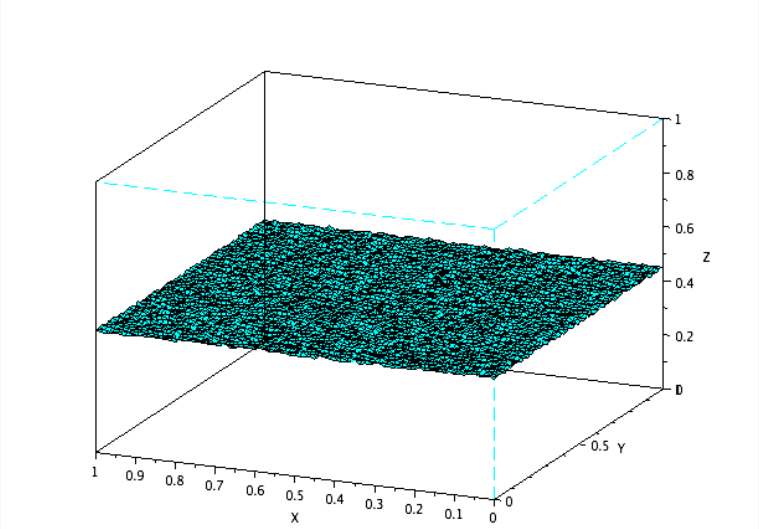


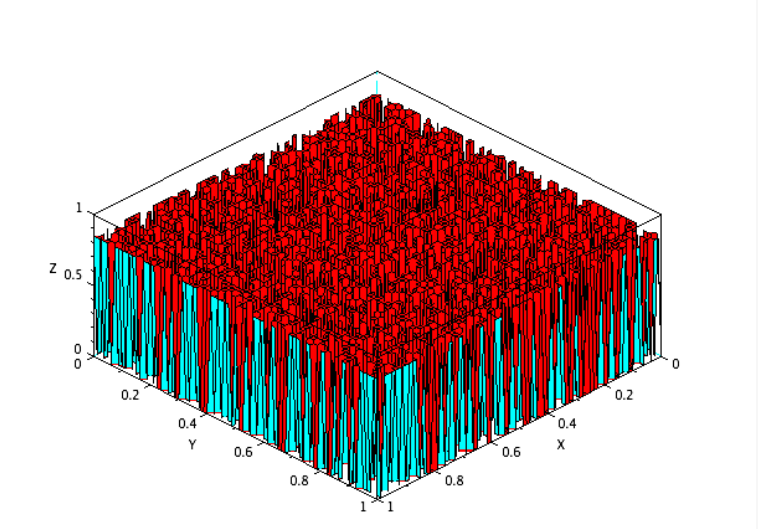
Numerical results #2

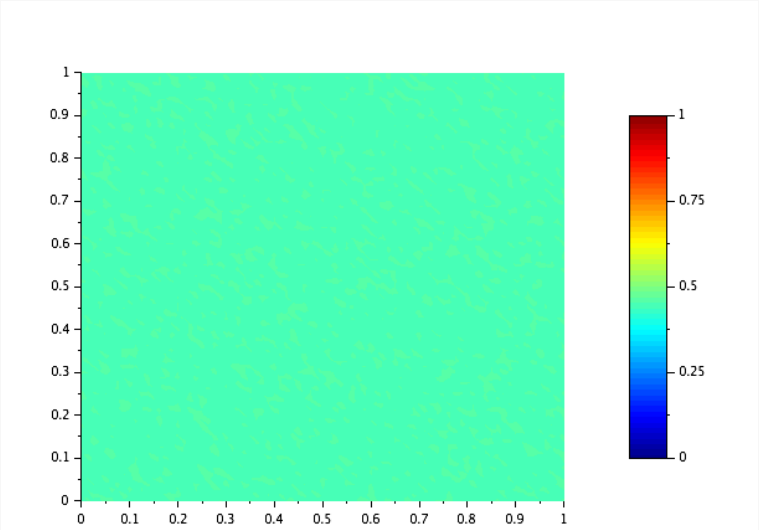


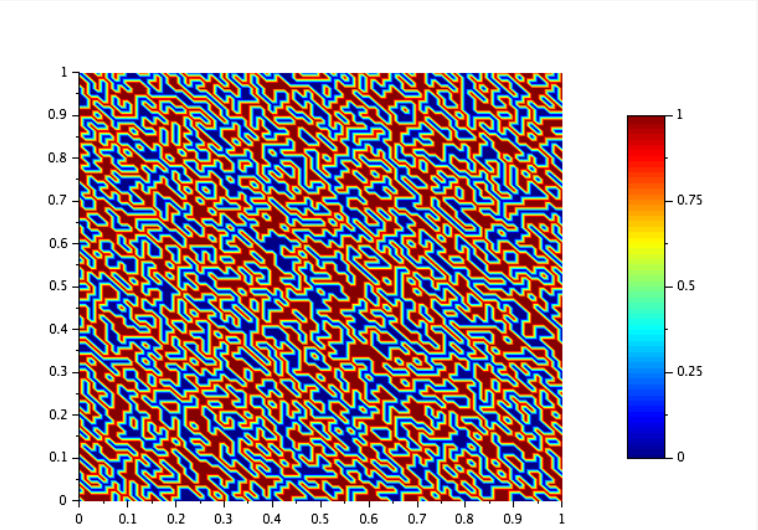
Initial data = centered perturbation of (u_0, v_0). Time $T = 200$, $a_0 = 0.005$, $\alpha = 2$.

Numerical results #2







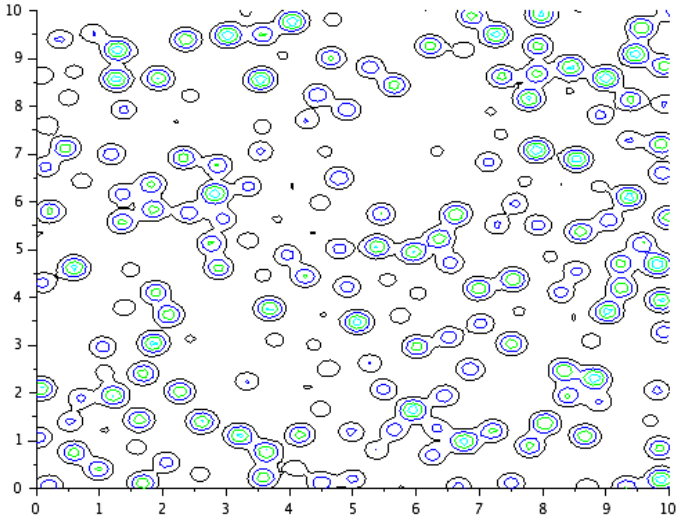


Initial data = uniform perturbation of (u_0, v_0). Time $T = 200$, $a_0 = 0.005$, $\alpha = 2$.

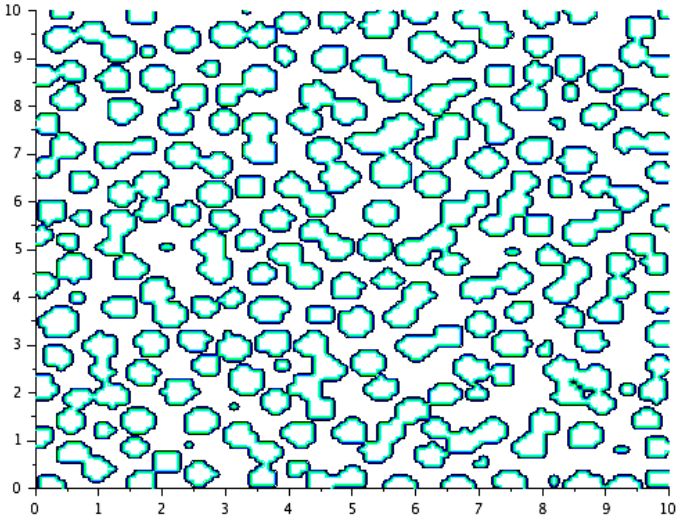
Initial distribution vs. final distribution

$\sigma = 3.3 \cdot 10^{-2} \ \frac{\mu m^2}{s}$, $a = 0.007$, $\alpha = 2.4$

$v_0 =$ sum of randomly distributed gaussian



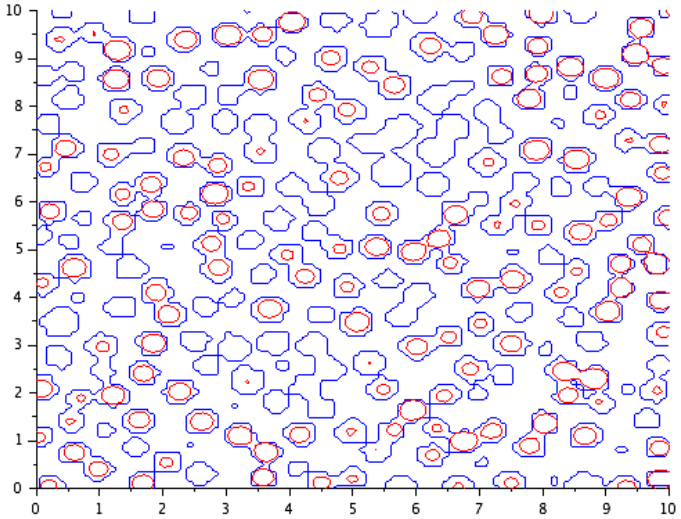
intial distribution

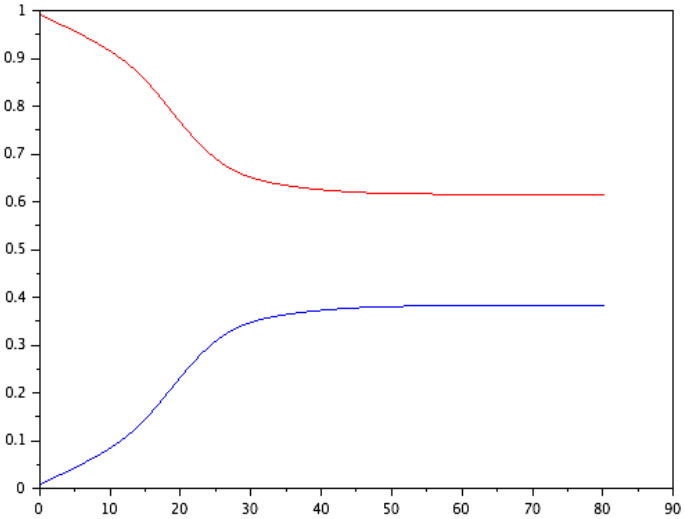


final distribution

- $\max(v_0) = 0.05$, $\min(v_0) = 10^{-5}$, $\max(v) = 0.96$, $\min(v) = 0.01$
- $\max(u_0) = 0.99$, $\min(u_0) = 0.95$, $\max(u) = \min(u) = 0.61$

Agregates growth





$$\text{contour } m = \frac{\max(v_0)+\min(v_0)}{2}$$

$$\text{contour } m = \frac{\max(v)+\min(v)}{2}$$

$$\text{Red line} = \int_\Omega u(T)\ dx\ dy$$

$$\text{Blue line} = \int_\Omega v(T)\ dx\ dy,$$

- At equilibrium 38% of cadherines are fixed and 62% are free to move.

Conclusions and Perspectives

- Linear aggregation functions do not leads to structure formations. Still, interesting mathematical problems concerning degenerate reaction-diffusion systems.
- Non-linear (sigmoids) aggregation and unbinding functions leads to Turing type instabilities. The choice of the parameters has to be investigated more deeply.
- To derive the mathematical model we need more biology experiments, in particular concerning the creation and growth of aggregates of cadherins in the absence of actin.

- Conclude the modeling and try to recover from numerics and mathematical results some biological information as the distance between aggregates and their mean size.
- Take into account the actin filaments and their influence on the distribution and behavior of cadherin aggregates.
- Study a discrete model (cellular automat) and/or hybrid models for the coupling with the actin filaments.

Thank you

Michèle

Philippe

Benoit

René-Marc

PEPS-Math-Bio-Info : MAC
Modélisation d'Adhesion des Cadhérines